CHAPTER 1

General introduction

AGEING POPULATIONS

Worldwide, populations are ageing[1]. Improvements in health care in the past century have contributed that nowadays people live longer[1]. One of the important challenges of present times is not only to prolong life expectancy, but also to improve the quality of life at older ages. Maintaining high cognitive functioning at older age is considered a key determinant of successful ageing[2]. It is well known that cognitive abilities decline as we age. A certain amount of this cognitive decline is a normal part of ageing. However, increased life expectancies worldwide will lead to an increase in the prevalence of dementia in the coming years[3]. In 2012, dementia was designated by the World Health Organization as major public health concern due to high prevalence rates and high economic and social burden of the disease[3] and many older adults fear developing dementia[4]. Moreover, dementia is indeed a major cause of death. In the United States dementia was estimated to be the third leading cause of death, after heart disease and cancer[5]. In 2013, the *Deltaplan Dementie* was launched in the Netherlands. In collaboration with the Dutch government, the industry, science, patient organizations, healthcare providers and insurers, the aim of the Deltaplan Dementie is to investigate ways to prevent and cure dementia, to improve dementia care and to create a dementia friendly society.

THREE STAGES OF COGNITIVE DECLINE

Cognitive functioning represents the mental ability to process and interpret information of daily life. It includes a variety of cognitive domains such as memory, attention, reasoning, planning of tasks and information processing speed[6]. It has been demonstrated that a decline in cognitive functioning already occurs at a relatively young age, resulting in a decline in multiple cognitive domains (i.e. memory, reasoning, phonemic and semantic fluency) over a period of ten years from the age of 45 years, although a faster decline was found in older people[7]. Some decline in cognitive function is considered to be part of normal ageing. However, there are great individual differences in the rate and timing of cognitive decline[8]. Accelerated cognitive decline and a deviation from population norms based on age and education level can be defined as cognitive impairment, with a classification of mild cognitive impairment (MCI) or dementia as result. Three stages of cognitive decline in the progression to dementia can be classified, starting with a preclinical phase in which subjective memory complaints (SMC) may develop, followed by mild cognitive impairments (MCI), and subsequently a diagnosis of dementia (Figure 1)[9].

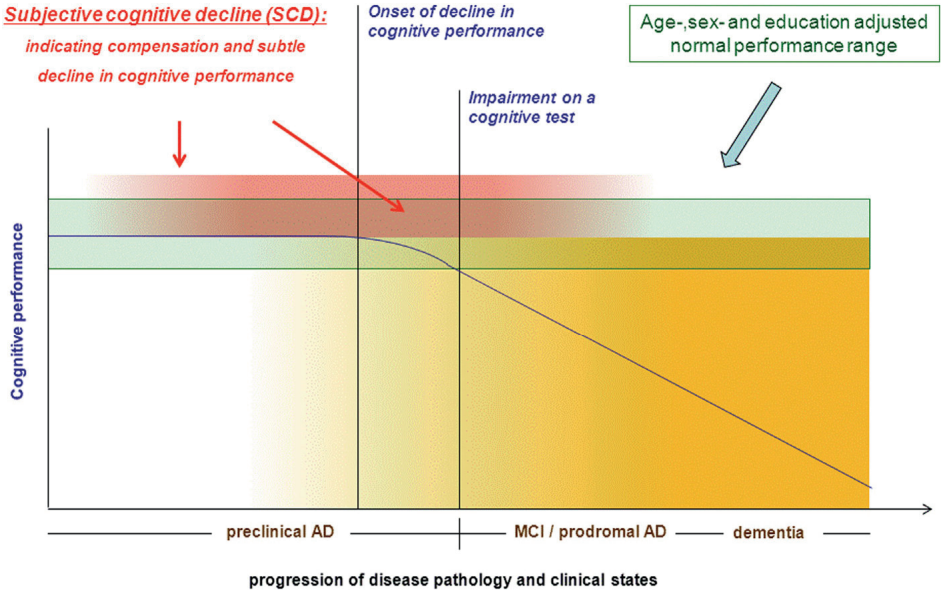

Figure 1. Progression of dementia pathology and clinical states (derived from Jessen at al. 2014[9]).

Dementia is a neurodegenerative disease characterized by a significant decline in cognitive functioning which interferes with the independency to conduct everyday activities. A diagnosis is generally made based on suboptimal performance in neuropsychological testing and subsequently classified according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)[10]. Alzheimer's disease (AD) is the most common form of dementia (50-75%) which has a gradual onset and is mainly characterized by memory impairments. Other forms of dementia are vascular dementia (20-30%), frontotemporal dementia (5-10%), and dementia with Lewy bodies (<5%)[11]. With the ageing population, dementia is becoming more prevalent, affecting over 46 million people worldwide in 2015. This number is estimated to increase to 131.5 million by 2050[12]. The occurrence of dementia increases exponentially with age, affecting approximately 5% of the population aged over 65, 20% at the age of 75+, and 50% at the age of 90+[13,14].

Dementia is often, although not always, preceded by *mild cognitive impairment (MCI)*. The term MCI is generally used to refer to a transitional stage between normal cognitive ageing and dementia[15]. The difference between dementia and MCI is on the determination of whether or not there is significant interference in independency to conduct everyday activities[16]. MCI is recently included in the latest DSM-5 criteria[10]. The most common type of MCI is the *amnestic MCI* in which a person shows subjective

and objective memory impairments with respects to age and education norms, but has no impairments in another cognitive function domain[17]. Patients diagnosed with amnestic MCI are particularly prone to progress to AD[18]. Depending on which definition is used, the prevalence of MCI among adults aged 65 years and older from the general population is estimated to be between 10% to 20%[19,20]. The risk of MCI increases with age[19]. Persons suffering from MCI often progresses to dementia, although certainly not all do. The base incidence rate of dementia among people aged 65 years and older from the general population is 1% to 2% per year. Whereas the progression rate from MCI to dementia is approximately between 6% and 10% per year[17]. However, studies also showed that 44% of patients with MCI at baseline returned to normal cognitive functioning one year later[21].

The development of dementia is gradual and brain changes underlying dementia are likely to develop over a period of at least 20 to 30 years before symptoms become noticeable[11]. *Subjective memory complaints (SMC)* may indicate the first symptomatic manifestation of dementia[9]. SMC have been associated with lower hippocampal volumes compared to those without SMC, even in subjects without objective cognitive impairment[22]. Commonly reported subjective memory complaints include difficulties in learning new names, recalling events that happened the previous day or two, retrieving the name of an old acquaintance, coming up with a specific word in a conversation, remembering why one walked into a room or certain direction, and remembering to take medications on time[23]. The prevalence of SMC among community-dwelling older persons is estimates to be between 25% and 50% and also increases with age[24]. It has been suggested that the stage of SMC lasts on average approximately 15 years before the subsequent stage of MCI is reached, with a progression rate of approximately 7% per year[25]. However, particular attention should be paid to the potential presence of depression, as depression is one of the strongest predictors of SMC[24,26].

PREVENTION OF COGNITIVE DECLINE

Due to the degenerative character of the disease and since interventions may be most effective in the preclinical stages of dementia, early detection of cognitive impairments is becoming increasingly important[27,28]. At present, there are no effective curative treatments for dementia. However, the extremely long time frame in the development of dementia provides a window of opportunity to slow down or maybe even prevent cognitive decline[13]. Higher age is the most important non-modifiable risk factor for late-life cognitive impairments[29]. Also genetics are important non-modifiable risk factors, such as the presence of the apolipoprotein E (APOE) ε4 allele. It has been estimated that 15% to 20% of dementia cases are attributable to this allele[30]. However,

in recent studies it has been suggested that up to a third of dementia cases could potentially be prevented through optimal regulation of modifiable risk factors including cardiovascular risk factors and diseases as well as improvement of educational level[31,32]. Another potentially important modifiable risk factor for incident dementia is poor social functioning. However, social functioning is generally insufficiently taken into account in order to determine its contribution to the risk of dementia. Genetic, vascular and lifestyle related risk factors often co-occur and interact across the lifespan to determine the risk of developing dementia in late life. This interrelation of risk factors is displayed in Figure 2. If interventions could delay the onset of AD by an average of two years, the worldwide prevalence of AD could be decreased by 22.8 million cases in 2050[33]. Costs for care in nursing homes and homes for the elderly constitute a major part of the costs of care for patients with dementia and prevention of cognitive decline can result in large economic savings[34].

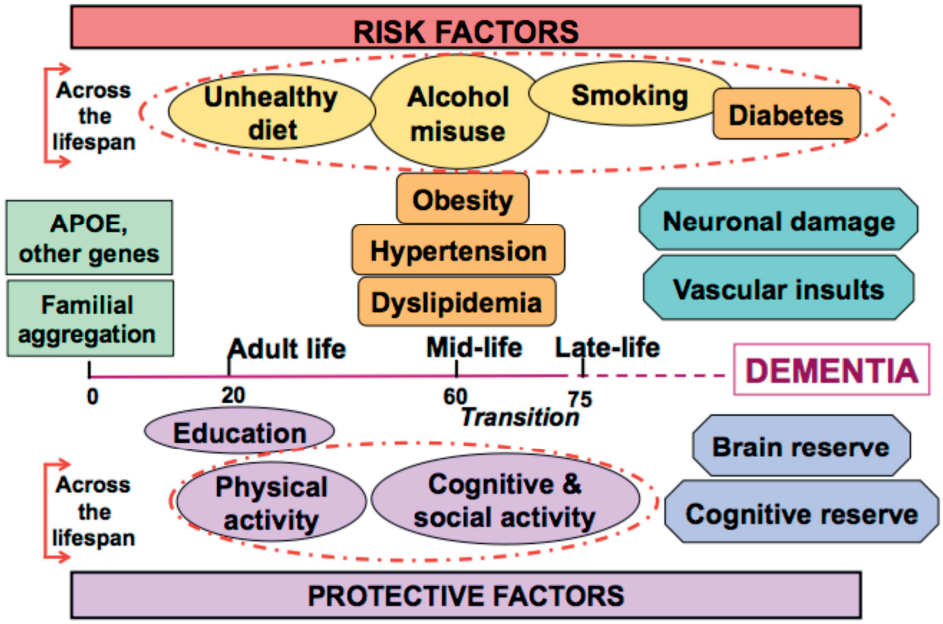

Figure 2. Risk factor for dementia across the lifespan (derived from Sindi et al. 2015[30]).

THE ASSOCIATION BETWEEN SOCIAL FUNCTIONING AND COGNITIVE DECLINE

Poor social functioning is suggested to be a potential risk factor for cognitive decline and dementia. However, the existing evidence on this association is inconclusive[35].

The few systematic reviews available summarizing the evidence on the association between social functioning and cognitive decline and incident dementia are contradictory on many aspects[6,35–42]. These reviews were hampered in drawing conclusions as the concept and operationalization of social functioning differed between the included studies[35]. For example, Fratiglioni et al. (2004) concluded in their systematic review that it was not possible to identify the effect of specific social activities. Therefore, Fratiglioni et al. (2004) did not specify specific social activities but applied more broad categories of social activities and networks[37]. In the research on modifiable risk factors for cognitive decline and the development of dementia, however, it has been shown that active engagement in mental, physical, and social activities are protective factors for cognitive decline and developing dementia[37,43]. However, many studies investigate the association between lifestyle and dementia, in which lifestyle represents a combination of mental, physical or social activities. This makes it difficult to specify the exact influence of specific social functioning factors[35]. Even in the case that only the association between social functioning and cognitive decline is investigated, often composite measures (e.g. a social vulnerability index[44], the Lubben Social Network Scale[45], or a graded sum score of the social network[46]) are used, which again makes it difficult to specify the exact influence of specific social functioning aspects.

Although poor social functioning has already been shown to be associated with higher risk of various adverse outcomes such as mortality[47], coronary heart disease[48], and depression[49], it remained unclear what specific contributions of the specific aspects of social functioning are in the process of cognitive decline. Therefore, the aim of this thesis is to evaluate the association between various social functioning aspects and the different stages of cognitive decline (i.e. SMC, MCI, and dementia). Furthermore, as we want to evaluate which specific aspects of social functioning are associated with cognitive decline, we investigate a broad range of social functioning aspects. The concept of social functioning is broad and includes many terms, such as social networks, social relationships, social ties, social support, and social integration[50]. As a consequence of this broad definition, the different terms for social functioning are used interchangeably in the literature[50]. In this thesis, the term social functioning is applied as an umbrella term for both simple objective quantitative aspects of social functioning, such as the number of social ties, marital status, or frequency of social contact, as well as more subjective qualitative aspects of social functioning which relate to the feelings towards the social relationships, such as emotional support and feelings of loneliness. Among individual studies that examined both quantitative and qualitative aspects of social functioning in relation to cognitive functioning, both aspects have been shown to be associated with cognitive decline, although the evidence is not conclusive (e.g.[51–55]). For example, one study found association between quantitative aspects of social functioning and cognitive decline but not for qualitative aspects[52]. Whereas other studies

found an association between qualitative aspects of social functioning and cognitive decline but not for quantitative aspects[51,54]. Another study reported no association with one of the social functioning aspects and cognitive decline[53], whereas another study showed an association between both quantitative and qualitative social functioning aspects and cognitive decline[55]. Similar to the distinction objective versus subjective, or quantitative versus qualitative, are two other commonly distinguished aspects of social functioning: 1) the structure of the social network (i.e. comparable to the objective quantitative aspects of social function), such as the size and the frequency of contact between the members of the social network, and 2) the function of the social network (i.e. comparable to the subjective qualitative aspects of social functioning), such as the perceived amount or quality of social support received from the network[50,51,56,57]. This distinction between structural and functional aspects is also applied in various parts of this thesis.

LIFELINES COHORT STUDY AND NETHERLANDS STUDY ON DEPRESSION IN OLDER PERSONS (NESDO) STUDY

Two studies in this thesis were based on data from the LifeLines Cohort Study[58,59]. LifeLines is a multi-disciplinary prospective population-based cohort study designed to examine in a unique three-generation design health and health-related behaviors. The cohort includes 167,729 persons living in the North of The Netherlands. Baseline assessment started in 2006 and was finished in 2013 and was performed in 12 local research sites. Participants are followed-up every 1,5 years with a questionnaire regarding demographics, health status, lifestyle and psychosocial aspects, and every five years with a physical examination including drawing blood samples, collecting urine samples, and cognitive performance.

Another study in this thesis was based on the data from the NESDO study[60]. NESDO was designed to examine the course and the consequences of depressive disorders in older persons (≥60 years). NESDO includes 378 depressed (according to DSM-IV criteria) and 132 non-depressed persons. The cohort consisting of depressed persons had assessments at baseline and at two and six year follow-up, whereas the normal controls (without depression) had assessments at baseline and one at two year follow-up. Data is collected on a broad range of determinants that might influence the course of depression in elderly people, including social and clinical determinants, life events, physical health, neurobiological determinants, cognitive functioning and the use of health care.

OBJECTIVES AND OUTLINE OF THIS THESIS

The overall aim of this PhD-thesis is to evaluate which aspects of social functioning are related to which specific stages of cognitive decline, starting from the end stage of dementia to the earliest signs of cognitive decline (SMC). First, in **Chapter 2** a systematic review and meta-analysis is performed to summarize existing literature on the association between social relationships and incident dementia in the general population. In **Chapter 3**, also by means of systematic review and meta-analysis, the association between social relationships and cognitive decline is investigated. In **Chapter 4** the relation between various aspects of social functioning and the development versus recovery of subjective memory complaints (SMC) is investigated within the LifeLines Cohort Study. Whereas the previous chapters include older adults from the general population, in **Chapter 5** the association between social functioning and cognitive decline among depressed older adults of the NESDO study is investigated. Since late-life depression is associated with both, poor social functioning and cognitive decline, we examined whether poor social functioning also predicts cognitive decline in depressed older persons. There is great diversity in tools measuring cognitive functioning. Therefore, in **Chapter 6** the measurement of cognitive functioning using a paper-and-pencil-test (Ruff Figural Fluency Test) is compared to the measurement of cognitive functioning using a computerized test (CogState). This project is conducted within the LifeLines Cohort Study. In **Chapter 7**, a general discussion of the findings reported in the above mentioned chapters are summarized and discussed. Furthermore, recommendations for future research are made.

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